REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 1-78, 79-97 and 110-115 were cancelled previously. Claims 116, 117 and 118, have been amended. Claims 101 through 109 and 116 through 118 are in the case and are before the Examiner.

I. The Amendments

Claim 116 has been amended to recite a sequence variation of no more than about 5 percent. Support for this amendment can be found at least at page 47 of the specification.

Claim 116(b) has been amended to clarify the meaning of the bracketed phrase so that the language of claim 116(b) resembles that of 117(d) and 118(d). Support for this amendment is found at least in claims 117 and 118. Claims 117 and 118 have also been amended to recite that the substitution is a conservative substitution. Support for this amendment can be found at least in claim 116, and at pages 46-48. The recitation of variant sequences has also been eliminated from claims 116-118. Specific support for these amendments can be found at least at pages 55-58.

Each of claims 116-118 has also been amended to recite the conditions under which the chimer particles enhanced stability are measured. Specific support for these amendments can be found at least in Example 6B that bridges pages 126-127 of the application. Claim 117 has also been amended to insert

the enhanced stability recitation that was inadvertently omitted in the last Reply. Specific support for that latter amendment can be found throughout the application as in the first full paragraph of the Summary bridging pages 7 and 8, the first of the benefits and advantages on page 12, the descriptions of Figs. 3, 4 and 8, the first full paragraph of the detailed description and throughout the specification.

It is thus seen that no new matter has been added.

II. The Action

A. Rejections Under 35 USC §112, Second Paragraph

It is noted with appreciation that the prior rejections based on the second paragraph of Section 112 have been withdrawn. The new rejection is discussed below.

1. "from the C-terminal residue of [the] HBc sequence" and "and within about 30 residues from the C-terminus of the chimer molecule"

The Action has raised a new ground of rejection based upon amended claim 116 and asserted that the amendments of the prior Reply necessitated the new rejection, thereby permitting the present final rejection. It is respectfully submitted that inasmuch as new claim 116 was a writing together of claims 1 and its dependent claim 98 as a new independent claim, the allegedly offending language was present in the original claims. As such, the finality of this rejection is improper because the rejection could have been made previously and is in fact new.

The impropriety of the finality of the rejection notwithstanding, the Action asserts that the first above-quoted phrase causes the claim to be indefinite because it "does not define what the specific position or residue of HBc the claim refers to since the C-terminal of the HBc is a region of amino acids." It can be agreed that a "specific position or residue of HBc" is not recited. However, it cannot be agreed that the claim is indefinite for that reason, and this basis for rejection is respectfully traversed.

Although the HBc portion of the chimer sequence can be of varying length, it has a C-terminal residue. Sub-paragraph (c) informs the reader that the chimer's C-terminal HBc residue is chosen from a position upstream (toward the N-terminus) from HBc position 150 by reciting that the sequence can contain "zero to about 100 amino acid residues in a sequence heterologous to HBc from position 150 to the C-terminus". (Emphasis supplied.) That HBc C-terminal residue could be, for example, HBc residue 140, 141, 142, 143, 144, or the like, as selected by the skilled worker.

The chimer can also have a non-HBc sequence attached to the HBc portion as noted above in sub-paragraph (c), and it is there that the second above-quoted phrase comes into play. That second-quoted phrase refers to the C-terminus of the chimer.

The complete sub-paragraph (b) relates to the position of the "C-terminal cysteine residue(s)" in the chimeric protein molecule, with that position being defined by the whole assertedly problematic phrase that is set out below.

> toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer

Thus, reading the whole phrase in context, one sees that the C-terminal cysteine residue(s) are in the direction of the C-terminus of the molecule from the C-terminal residue of the HBc sequence portion of the chimer; i.e., downstream from the last of the HBc residues, and within about 30 residues of the C-terminal end of the chimer molecule.

It is respectfully submitted that there is nothing indefinite about the recitation. A worker of ordinary skill to whom this disclosure is addressed should have no difficulty understanding the wording.

B. Rejection Under 35 USC §112,
First Paragraph

Withdrawal of the rejection of cancelled claims 98-100 is noted with appreciation. The present Action has maintained the previous rejection as to claims 101-109 and extended that rejection to claims 116-118. Thus, all of the currently pending claims were rejected under the first paragraph of Section 112 as the specification was allegedly being non-enabling in regard to the breadth of the claims that could encompass a sequence whose polypeptide chain was 80% similar to HBc.

It cannot be agreed that at the time the parental and present applications were filed that a skilled worker would have any difficulty in making or using any construct of the claims, as that is the requirement under *In re Angstadt and Griffin*, 190 USPQ 214, (CCPA 1976). In *Angstadt*, the Court

held that the question of enablement revolves around whether the

> "disclosure contains sufficient teaching regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention" [190 USPQ at 218; emphasis in the original.]

That Court went on to discuss the disclosure that there taught how to make and how to use a claimed catalyst. It continued that if a skilled worker wanted to make another catalyst than those specifically disclosed in the 40 examples that worker could simply follow the disclosure and make a desired catalyst compound. It further pointed out that the catalysis process was not complicated and needed no special conditions nor equipment. The *Angstadt* claims were found to be enabled despite the amazingly large number of catalysts encompassed.

That Court went further in saying that some "experimentation" was permitted and held that the key phrase was "undue", not "experimentation". Practicing of that invention "would not 'require ingenuity beyond that to be expected of one of ordinary skill in the art' ... ", at 218 (citation omitted). The same should be the case here.

In re Wands, 8 USPQ2d 1400, (Fed. Cir. 1988), a case noted in the Action, involved time-consuming monoclonal antibody preparation and screening, biological and biochemical processes. There, the Court found that practitioners of the art were prepared to screen negative hybridomas. A similar finding was made in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, (Fed. Cir. 1986). Those familiar with the

hybridoma/monoclonal antibody art know that such preparations and screenings often involve months to generate antibodies and thousands of assays. Those procedures are nevertheless well known, accepted and routine in the art.

In the context of the description requirement, the Federal Circuit has held that "an amino acid sequence supports 'the entire genus of DNA sequences' that can encode the amino acid sequence because the 'state of the art has developed' such that it is a routine matter to convert one to the other." [*Capon v Eshhar*, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005) citing *In re Wallach*, 71 USPQ2d 1939 (Fed. Cir. 2004).] It is submitted the making and using of nucleic acids as are used here is no less developed.

The Actions have asserted a lack of guidance, working examples and an unpredictable nature of the art. However, the Actions have provided no evidence of a need for guidance greater than that provided in the specification, nor unpredictability to a degree that would lead to a lack of enablement. In addition, the courts have said working examples are unnecessary [*In re Strahilevitz*, 212 USPQ 561 (CCPA 19982)].

The above notwithstanding, the claims have been amended to moot the rejection so as to speed prosecution. It is believed that the previously discussed amendments that recite that a chimer contains "no more than about 5 percent' substitutions in sequence, as well as eliminating variant sequences have made moot this rejection.

The Examiner's attention is also invited to the disclosures of US Patent No. 6,964,769 to Sebbel et al., that just came to counsel's attention and is noted on enclosed Form

PTO/SB/08A. Claim 1 and all of the dependent claims of that presumptively valid patent recite a named polypeptide sequence "or a sequence having at least 90% sequence identity to said polypeptide sequence . . ." Counsel was unable to find any disclosure as to the identity of the up to 10% substituting residues, as compared to the lower percentage of substitutions in the amended claims herein. It is thus submitted that the present claims define a more limited number of chimers than those of the presumptively valid issued patent that claims similar, but different chimers. It is therefore submitted that Dr. Birkett was in possession of a very large number of the desired chimer molecules as of the filing date, and that this portion of the rejection should be withdrawn.

C. Rejections Under 35 USC §102(b)

(1). Zlotnick et al.

Withdrawal of the rejection of claims 98-101, 103, 105, 108 and 109 pursuant to 35 USC §102(b) as anticipated by Zlotnick is noted with appreciation. That rejection has, however, been maintained as to claims 102, 106, 107 and extended to claim 117. This rejection is respectfully traversed as discussed below.

The gist of the present Action is that the nucleic acid of claim 117 can encode a polypeptide that contains an added C-terminal cysteine but no added, heterologous epitope. As such, the third "new" Zlotnick construct that was C-terminally truncated to position 149, had the three alanines replacing the three internal cysteines, as well as an added

cysteine at residue position 150 that is denominated Cp*150 anticipated the claimed subject matter.

That Cp*150 structure had substitutions of alanine for cysteine, but those substitutions were said to be within "nucleic acid sequence that encode peptides [that] have more than 80% similarity to HBc." It is submitted that present and prior claim 117 recites that only 5 percent of the HBc residues can be substituted. In addition, those permitted substitutions must be conservative. It is submitted that a Cys-to-Ala substitution is not a conservative substitution. It is thus further submitted that the present claim is not anticipated by the Zlotnick disclosure, and that this rejection should be withdrawn.

2. Yoshikawa et al.

Withdrawal of the rejection of claims 98-109 based on the Yoshikawa disclosures is noted with appreciation.

D. Rejection Under 35 USC §103(a)

1. Pumpens in view of Zlotnick

Claims 100-109 and 115-118 were rejected as allegedly obvious over the disclosures of IDS document A16 by Pumpens in view of Zlotnick, as in the prior Action. This rejection is respectfully traversed as discussed below.

The present and prior Actions have selected from the art only so much as would seem to make a *prime facie* case based on a hindsight reconstruction of the claimed subject matter, while neglecting to examine the teachings of the art as a

whole, as is required by the Court in *Panduit Corp. v. Dennison Manufacturing Co.*, 227 USPQ 337, 344-345 (Fed. Cir. 1985) and the cases cited therein. As the Court said,

> [i]n its consideration of the prior art, however, the district court erred . . . in considering the claims in less than their entireties . . . and in considering the references in less than their entireties, i.e., in disregarding disclosures in the references that diverge from and teach away from the invention at hand. . . .
> * * * * * *
> * * * * *
> *
> The result is that the claims were used as a frame, and individual naked parts of separate prior art references were employed ass a mosaic to recreate a facsimile of the claimed invention. [Quoting *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 USPQ 303, 311-312 (Fed. Cir. 1983).]

Thus, Pumpens teaches that "capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles." That statement was echoed by the later-published Borisova paper of prior Exhibit 1 that states near the top of the right-hand column of page 18 "HBcΔ (C-terminally-truncated HBc particles) were less stable than the corresponding full-length protein particles." Those teachings are agreed with and echoed also in the present application.

However, great weight is placed on the Pumpens disclosure that foreign insertions internal to the HBc sequence "also exert an stabilizing effect on chimeric HBCΔ (sic) derivatives" even though the basis for that statement is unpublished work by Borisova whose later-published paper dealt

with such internal insertions into HBc, but reported no enhancement of stability. The present Action asserts that the Pumpens paper was a

> written record. Any published statements, suggestions, opinion, written records, etc, reflect the state of the prior art and knowledge of one of skill in the art, and can be used for assessing the obviousness of an invention at the time the invention was made. (Action, page 5, Paragraph 14.)

Unfortunately, that argument here is misplaced. It is submitted that that Pumpens/Borisova disclosure of stabilization through internal insertion is actually helpful here because it leads away from the present invention whose active agent gains stabilization from an added C-terminal cysteine.

In addition, the argument is also misplaced because the present disclosure and claims are directed to those of skill in the art. It is submitted that a skilled worker here has a PhD or MD degree, or both, several years of experience as a leader of a research group of several advanced degreed workers, and has published several papers as a sole or lead author. Such people tend to not believe work that is attributed to a worker who, having the opportunity, failed to corroborate the assertion made by another. That is particularly the case where such a worker can examine the data in this application and make up his/her own mind about the veracity of the statement from another set of data.

Still further, the Schödel papers discussed in the paragraph bridging pages 6 and 7 of the specification (IDS documents A15 and A27) note the instability observed with

C-terminally-truncated HBc proteins that contain insertions in their sequences as is claimed herein. Those papers were published in refereed journals and should be given greater weight than Pumpens' aside to Borisova. As was noted previously, if Pumpens/Borisova were correct, the problem of instability would have been solved by inserting foreign sequences. At the least, there are conflicting teachings and each disclosure "must be considered 'for its power to suggest solutions to an artisan of ordinary skill. . . . considering the degree to which one reference might actually discredit another'" [*Medichem S.A. v. Rolabo S.L.*, 77 USPQ2d 1865,1870 (Fed. Cir. 2006) citing *In re Young*, 18 USPQ2d 1089 (Fed. Cir. 1991).]

Of course, had the instability problem been solved as suggested by the Action or as suggested by Pumpens, the problem alluded to in the application at page 7 and noted in Ulrich et al., *Adv. Virus Res.*, vol.50 (1998) Academic Press pages 141-182 (IDS document A28), concerning "the requirement of reproducible preparation of intact chimer particles that can also withstand long-term storage" would have been met and Ulrich, writing three years after Pumpens, would have been mistaken. Ulrich cites the relied-on Pumpens paper, but still notes that stability of truncated, chimeric particles is missing in the art. Indeed, at page 164, Ulrich states:

> [t]he stability of chimeric HBcAg particles under storage conditions has not been analyzed in detail; whereas C-terminally truncated HBcAg particles were reported to require storage at -70°C to preserve stability . . . (Citation omitted.)

The Examiner's attention is also invited to the paper by Zhou and Standring that was cited in the prior Action. That paper, Zhou et al., *J. Virol.* **66(9):**5393-5398 (Sept 1992; hereinafter Zhou), discussed results obtained with full length HBc whose four native Cys residues were exchanged for Ala residues, as well as similarly Ala-for-Cys mutated C-terminal-truncated constructs ending with residues 149 and also 172. That paper reported that

> Cys residues and disulfides are not required for the assembly of either HBV capsids or the dimers that provide the precursors for capsid assembly. . . . Cys residues stabilize isolated p21.5 structures, as evidenced by the marked reduction in stability of Cys-minus dimers and capsids . . . (Abstract)

The Zhou paper thus is substantially similar in its disclosures to the disclosures of Zlotnick in regard to the effect of the Cys residues on stability of particular constructs, although Zlotnick did not cite the Zhou paper. The relied-on Pumpens paper cited Zhou as did the above Ulrich paper. The Zhou and Zlotnick papers were also cited in an otherwise redundant review by Pumpens and Grens, *FEBS Letters*, **442**:1-6 (1999), enclosed as Exhibit 1 and noted on Form PTO/SB/08A.

Notwithstanding the fact that skilled workers Pumpens and Ulrich not only knew of the Zhou and Zlotnick papers, but cited them, neither group of skilled worker authors put together the earlier Pumpens paper with either of those disclosures to solve the problem of stability as has the present inventor. Here were workers of at least ordinary skill in this art, if not greater than ordinary skill, and they did

not do what the Action has asserted would have been obvious to a mere worker of ordinary skill.

It is submitted that once the disclosures of the art as a whole are taken into account, the aside to the Borisova unpublished work would be given little weight by a skilled worker, or if not all together disregarded, that disclosure would have been found confusing and non-directional in view of the contrary disclosures of Ulrich and Schödel. Such a worker would still be looking for an answer to stability when the claimed invention was made and this application was filed. It is further submitted that the only way a worker of any skill in this art would have come to the presently claimed invention would have been by a hindsight reconstruction after reading the present specification and claims. Such a hindsight reconstruction is impermissible in assessing patentability under Section 103, and this rejection should be withdrawn.

E. Provisional Double-Patenting Rejection

Withdrawal of the provisional double-patenting rejection in view of the filed Terminal Disclaimer is noted with appreciation.

F. Priority

A corrected application data sheet, page 4, is enclosed pursuant to the Examiner's helpful suggestion.

H. Summary

Claims 116, 117 and 118have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

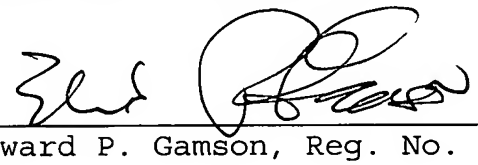
It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

A Petition for an Extension of Time of one month and its required fee as a large entity are enclosed to permit the Examiner extra time to consider this paper.

No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 

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Enclosures
- Form PTO- SB/08A, art
- Amended Application Data Sheet, page 4
- Petition and Fee for One-Month Extension of Time

CERTIFICATE OF MAILING

I hereby certify that this Reply and its stated enclosures are being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: MAIL STOP AF, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on September 19, 2006.

By _____
Edward P. Gamson